Draft Structured Product Labeling Implementation Guide for FDA Content of Labeling

Version No.	Date of Change	Changes Made to Version
0.9	20060728	Combines information from the two previous IG Clarifications and corrections from Highlights IG Remove <title> element for entire SPL Add inclusion of Author tag Add emphasis as styleCode Describe Highlights "boilerplate" information Describe ingredient strength conventions Add ingredient strength range

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1. Introduction

This document provides technical details on using Structured Product Labeling (SPL) for FDA Contents of Labeling for Human Prescription Drug and Biological Products. The scope in this document is limited to the SPL used for FDA Content of Labeling. Additional data elements that are not covered in this document are not part of the FDA Content of Labeling at this time and are outside the scope of this document. Instructions related to the information to include in the Contents of Labeling are also outside the scope of this document. Details on controlled vocabulary referred to in this document are on the FDA Data Standards Council web site at http://www.fda.gov/oc/datacouncil.

2. SPL Header

2.1. Stylesheet and schema location

Information: This information includes the location of the current stylesheet for the FDA view of the SPL and the location of the current schema.

Terminology: None

SPL location: This information is in the beginning of the SPL file.

XML details: The instructions at the start of SPL are the same for every SPL document and are in the following form:

```
<?xml version=”1.0”?>
<?xml-stylesheet href="http://www.fda.gov/oc/datacouncil/stylesheets/spl/spl.xsl" type="text/xsl"?>
<document xmlns="urn:hl7-org:v3" xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:schemaLocation="urn:hl7-org:v3 http://www.fda.gov/oc/datacouncil/schemas/spl/spl.xsd">
```

2.2. SPL identifying information

Information: This information provides basic information for identifying the SPL document.

Terminology: The type of content of labeling is from LOINC.

SPL location: This information is in the beginning of the SPL file.

XML details: The identifying information is in the following form:

```
<id root="xxxxxxx-xxxx-xxxx-xxxx-xxxxxxxxxxxx"/>
<code code="xxxxx" codeSystem="2.16.840.1.113883.6.1" displayName="xxxxx"/>
<effectiveTime value="yyyymmdd"/>
```

```
<setId root="xxxxxxx-xxxx-xxxx-xxxx-xxxxxxxxxxxx"/>
<versionNumber value="x"/>
```

- The <id root> is a globally unique identifier (GUID) for the specific document SPL instance and will differ for every regulatory submission.
- The <code> is the LOINC code for the type of content of labeling such as "Human Prescription Drug Labeling with Highlights".
- The effective time is the revision date and includes the year, month, day as yyyymmdd.
- The <setID> is the unique identifier for the document that remains constant through all versions/revisions of the document.
- The <versionNumber> is an integer that identifies the version of the document and along with the <setId> is unique for each version of the product label.
- Note that the <title> data element is not used as the title for the labeling is generated by the stylesheet from the data elements and includes the proprietary name, non proprietary name, dosage form, strength, route of administration, DEA schedule, if applicable, and company name.

2.3. Company information

Information: Highlights includes the company name and contact information (phone number, web site) for reporting suspected drug adverse reactions. Company name is also included in the title.

Terminology: There is no controlled terminology for this information.

SPL location: This information is captured in the SPL general header elements.

XML details: The name of the company is represented in the <legalAuthenticator> child of the <document> element. The direct <telecom> children of the <assignedEntity> element are the contact phone numbers and URL for reporting adverse reactions. Note that more than one <telecom> element is permitted as a child of <assignedEntity> , e.g., a phone number and web site URL as separate <telecom> entities.

The following is representative coding for <legalAuthenticator>:

```
<document>
   …..
   …..
    <legalAuthenticator>
        <time/>
        <assignedEntity>
            <telecom value="place the adverse reaction contact phone number here"/>
            <telecom value="place the adverse reaction contact url address here"/>
            <representedOrganization>
                <name>company name here</name>
            </representedOrganization>
        </assignedEntity>
    </legalAuthenticator>
</document>
```

Definitions of elements:

1. <telecom> child of <assignedEntity>: the <telecom> element may be used more than once, however, the first instance should provide the phone number to be used for reporting adverse reactions.
2. <name> child of <representedOrganization>: This should contain the name of the organization as it appears in the Highlights.
3. Other elements such as address are not included.

The name of the company for the product labeling title is represented in the <author> child of the <document> element. The following is representative coding for <author>.

```
<document>
   …..
   …..
    <author>
        <time/>
        <assignedEntity>
            <representedOrganization>
                <name>company name here</name>
            </representedOrganization>
        </assignedEntity>
    </author>
</document>
```

2.4. Year of Initial US Approval

Information: Highlights provide the 4 digit year (not day or month) of the initial US approval.

Terminology: There is no controlled terminology for this information.

SPL location: This information is captured in the SPL general header elements.

XML details: The 4 digit year of initial US approval as it should appear in Highlights is contained in the <time> child of the <verifier> element. For example:

```
<verifier>
    <time value="2005"/>
    <assignedEntity/>
</verifier>
```

3. SPL Body

Information: The SPL body includes the Full Prescribing Information (FPI), Drug Listing data elements, Highlights text and Highlights data elements, as appropriate.

Terminology: LOINC is used for the sections and subsections codes.

XML details: In addition to SPL header information, the <document> element contains a required <component> which contains the <structuredBody> element. The <component><structuredBody> tags enclose the body of the SPL document; the body consists of the human readable content of labeling (text, tables and figures) plus structured data elements (e.g., Drug Listing data elements) including both human readable and machine processing content.

4. FPI Sections and Subsections

Information: Sections and subsections have titles and codes.

Terminology: LOINC codes are used for sections and subsections codes.

SPL location: The title and LOINC codes are associated with the section and subsection.

XML details: The <title> of the sections and subsections and order of the sections and subsections as they appear in the SPL are used to render the FPI Contents. The section <title> and subsection <title> are rendered as bold. The numbering for the sections and subsections are included in the <title> text.

In the SPL schema, the <structuredBody> element contains multiple <component>s, and each <component> contains a <section>. Sections are used to aggregate paragraphs into logical groupings. For the FDA implementation of SPL, <section>s defined by the labeling regulations in 21 CFR 201.56 and 57 (e.g., Indications and Usage) are assigned LOINC codes. These sections are expected to be coded with the appropriate LOINC code in SPL. Sections that have not been assigned a LOINC code have the option of not being assigned a code (i.e., does not contain the <code>) or may be assigned the LOINC code for an unclassified section.

The order in which sections appear in an SPL document is the order the sections will appear when displayed (rendered) using the standard stylesheet and are defined by the labeling regulations in 21 CRF 201.56 and 57. Each section has a unique identifier (<id>), may be identified semantically by a LOINC code (i.e., the <code> element), and may contain a <title>.

The human readable content of labeling is contained within the <text> element in the <section>. The <section> can be nested to form sub-sections. The schema for subsections in SPL requires that the nested <section> tag first be nested inside a <component> tag. Use nested sections to relate paragraphs. The section tag applies to all of the nested sections. By nesting sections, computer systems can use the section tags in SPL to display information useful for the care of patients. If information is not associated with the tag, it will not be displayed.

Using the following principles for markup of text information improves access to information in labeling:

- Use the <title> element to capture the section heading that appears in the label instead of placing the text of the title within the <text> element. This allows computer systems to use and display this information properly.

- Use assigned section tags even when the printed label does not include a heading. For example, tagging a pregnancy statement as a section in a label that does not have a heading for pregnancy is useful. Computer systems will be able to use the tag to capture the pregnancy use statement. Omitting the <title> would prevent the heading from appearing when the SPL is rendered.

- Use the ID attribute to the <section> element, e.g., <section ID="Clin_Pharm_Section”> if the section is to serve as the target of a <linkHtml> element. Linking to the ID attribute of a section allows the link to 'reference' the section entirely, e.g., for retrieval of a whole section in a non-browser interface.

5. FPI Text

Information: This is the human readable content of labeling.

Terminology: There is no controlled terminology for this information.

SPL location: This is provided in the appropriate sections and subsections of labeling.

XML details: The human readable content of labeling (the narrative) is contained within the <text> element. The actual content is contained within a <paragraph>, <table>, and/or <list>. If a section consists only of nested sections, the <text> tag is not included. Elements that can be used within the <text> element to capture the human readable content of SPL include paragraphs (<paragraph>), lists (<list>), tables (<table>) and images (<renderMultimedia>). Elements permitted as children of the <text> element, used as children of the <paragraph> element or within <table> and <list> include superscripts (<sup>), subscripts (<sub>), links (<linkHtml>), line breaks (
), footnotes (<footnote>), footnote references (<footnoteRef>). Images may be included in the content of labeling using the <renderMultiMedia> tag. This tag may be used as a direct child of <text> for ‘block’ images or as a child of <paragraph> for inline images.

5.1. Font Effects

There are certain aspects of the rendering of SPL that must be specified in the SPL source to insure that the content of labeling is formatted correctly when rendered. For example:

<paragraph>The next snippet <content styleCode="bold italics”> will appear as bold italics</content> in the rendering.</paragraph>

Will be rendered as:

The next snippet ***will appear as bold italics*** in the rendering.

The <content styleCode=””> can also be nested, for example:

<content styleCode="bold italics”> will appear as bold italics</content>”

Can also be represented as:

<content styleCode="bold"><content styleCode="italics"> will appear as bold italics.</content></content>

Attribute values for <styleCode> for font effect includes bold, italics, underline. When font effects are used to emphasize text such as text in a box warning, the <styleCode="emphasis"> is used in addition to the font effect <styleCode>. A special <styleCode> is used for recent major changes (see below).

5.2. Symbols and special characters

Special characters can be included in narrative (i.e., the text content) or the header <title> and may be created in different ways. Simple superscripts and subscripts are accomplished with tagging included in the SPL schema, i.e., <sup> and <sub> tags. Unicode character references are used for special characters. Unicode characters in SPL XML are inserted as either &#dddd; where dddd is the Unicode value (for decimal values) or &#xdddd; when hexadecimal values are used. The font used in the standard stylesheet is a Unicode font assuring that Unicode values in SPL content will be rendered correctly if viewed by a browser supporting this font. Also note that because SPL XML tags begin with the less than symbol (<), use of this symbol in text content must be replaced by the XML entity &lt e.g., "<paragraph>. The mean for group 1 was < 13. </paragraph>" will render as "The mean for group 1 was <13."

5.3. Footnotes

The SPL schema includes a specific footnote element <footnote>. Footnotes are rendered automatically by the standard SPL stylesheet. <footnoteRef> is used to refer to another (usually earlier) footnote. For example,

<footnote ID="testNote">This is the footnote content</footnote>

Will generate the following footnote:

[6] This is footnote content

at the appropriate end of a section.

The <footnoteRef> element with the appropriate IDREF attribute, e.g., <footnoteRef IDREF="testNote"/> will display the footnote reference in the text corresponding to the footnote with the same ID, e.g., in this example footnote 6.

Footnotes are rendered by the default stylesheet using Arabic numbers (e.g., 1,2 3,). Within tables, footnotes are rendered using footnote marks in the series: * † ‡ § ¶ # ♠ ♥ ♦ ♣, effectively separating numbered footnotes within general text and footnotes within tables. Footnotes within tables are rendered at the bottom of the table.

5.4. Lists

All lists are marked up using the <list> tag, and each item in a list is marked with an <item> tag. The 'listType' attribute identifies the list as ordered (numbered) or unordered (bulleted). The default numbering and bulleting are controlled by the stylesheet.

Lists featuring a standard set of specialized markers (standard specialized lists) can be created using the styleCode attribute with the <list> element. Options available for ordered lists are:

- Arabic (List is ordered using Arabic numerals: 1, 2, 3)
- LittleRoman (List is ordered using little Roman numerals: i, ii, iii)
- BigRoman (List is ordered using big Roman numerals: I, II, III)
- LittleAlpha (List is order using little alpha characters: a, b, c)
- BigAlpha (List is ordered using big alpha characters: A, B, C)

For example: <list listType="ordered" styleCode="LittleRoman">

For unordered lists the following options exist:

- Disc (List bullets are simple solid discs: ●)
- Circle (List bullets are hollow discs: ○)
- Square (List bullets are solid squares: ■)

For example: <list listType="unordered" styleCode="Disc">

In addition to the standard specialized lists, user-defined characters are also permitted as markers by nesting <caption> within the <item> tag. Note that any character, XML entity, or Unicode symbol, may be used in the <caption>, and that the <caption> for each <item> are not restricted to the same character.

For example: <item><caption>*</caption> the asterisk is used as item marker here.<item>

5.5. Tables

Tables can be created with the full structure (header, body and footer). The element <tbody> is required for an SPL table while the elements <thead> and <tfoot> are optional in the SPL schema. The structure will display a standard typographical table with rules between the caption (table title) and head, the head and body, and the body and <tfoot>. If a <tfoot> element is included and footnotes are present in a table, then footnotes are rendered after the existing content of the <tfoot> element.

It is recommended to always start with a standard table (i.e., <thead> and <tbody> elements) and test to see whether the rendering is unambiguous and interpretable. It is important that the table communicate labeling content not that it duplicates the presentation in word processed or typeset versions of the package insert. In the unusual situation where additional formatting is needed, the rule styleCode specified may be used to modify the table.

The rule codes are as follows (note that the control names are case sensitive).

- Rule on left side of cell is Lrule
- Rule on right side of cell is Rrule
- Rule on top of cell is Toprule
- Rule on bottom of cell is Botrule

Note: More than one rule control may be used in a cell, e.g., <td styleCode code=”Botrule Lrule”>Cell content </td>.

Rule control codes should be used only when necessary for the interpretability of the table. Use of these codes may result in overriding the default rules for tables. Rather than setting the rule for each cell, table rules may also be controlled according to entire rows or columns by use of the styleCode attributes with <col>, <colgroup>, <thead>, <tfoot>, <tbody> and <tr> elements.

To make rowgroups appear with horizontal rules, use the styleCode attribute "Botrule" with the appropriate <tr> element. The Botrule value is rarely needed on the <td> element.

The preferred method for using vertical rules is to define colgroup with styleCode="Lrule” or “Rrule" (or both). Only if this does not yield the desired vertical rule should the Lrule or Rrule code value with styleCode attributes on the <td> or <th> element itself be used. Note: In general, vertical rules should not be used. Good typography for tables means using few vertical rules.

For horizontal alignment, the preferred method for aligning cell content within the margins is to use <col align=”.. ”/> in the <colgroup> element, though this can be used in the <colgroup> element as well. Valid values for align are “left”, “center”, “right”, “justify” (for full justification of contents within the cells), and “char” (for character alignment within the cells). Using the <col align=”.. ”/> markup ensures that the contents for all cells in the column share the same alignment.

For vertical alignment, the valign attribute can be used within cells. For cases in which the cell alignment must be different from other cells in the column, align is also available as an attribute on the other table elements, including <td>.

Markup for table footnote is rendered in the <tfoot> tag. This element does not need to be included in SPL; the standard stylesheet will include a <tfoot> tag if a <footnote> element is present within either the <thead> or <tbody> sections. A <tfoot> section should be included in SPL only if there is additional information other than footnotes that needs to be rendered in this section.

For table text spacing, in some instances, the use of a “tab” or text indentation is desirable in a given table cell. In an SPL document, this effect is achieved by using the nonbreaking space ( ) as if it were a “tab” space. As the following snippet of XML shows, two nonbreaking spaces were used to offset the word “Male” from the margin: <td> Male</td>. The nonbreaking space can also be used to keep text in a table from breaking inappropriately due to browser resizing.

5.6. Image

The SPL schema uses <observationMedia> elements to identify graphic files to be rendered at the locations where they are referenced by <renderMultiMedia> elements in the <section>. In other words, an image in an SPL will be rendered wherever it is referenced by the renderMultimedia markup, no matter where the observationMedia markup appears. The referencedObject attribute of the renderMultiMedia element identifies the corresponding observationMedia instance by means of its ID identifier such as <renderMultiMedia referencedObject="MM1"/>

The <observationMedia> element does not contain the graphic file, but instead points at the file. The observationMedia identifies the graphic media type (e.g., JPEG). In addition, the observationMedia element includes the text description of the image used by screen reader software for visually impaired users. This is included in the <text> child of <observationMedia>. Note also that observationMedia is always contained within a <component> element as illustrated below.

```
<component>
    <observationMedia ID="MM1">
       <text>Descriptive text here<text>
       <value xsi:type="ED" mediaType="image/jpeg">
          <reference value="drug-01.jpg"/>
       </value>
    </observationMedia>
 </component>
```

For image placement, if an image is a block image (i.e., should appear in its own space), insert the renderMultimedia tag after the closing </paragraph> tag. If an image is inline (i.e., should appear alongside text), insert the renderMultimedia tag in the text of a <paragraph> as appropriate. Inline images are expected to be uncommon and basically represent symbols that cannot be represented by Unicode characters. In addition, <caption> are not applicable for inline images since these are not offset from the surrounding text.

The SPL schema does not allow for resizing graphics or changing the resolution of graphics files. Thus, all images are rendered in the browser as-is, with all characteristics of the actual graphic file itself. To ensure that a graphic will appear as desired, it is very important that the graphic file is edited to a dimension appropriate for its presentation within the browser. If this is not done, the appearance of the graphic may not be consistent with the narrative content reducing the readability of the file.

The JPEG image file type for images should be used for appropriate viewing in a browser using the standard stylesheet.

5.7. Hypertext Links

SPL offers hypertext linking capabilities generally similar to those found in the HTML specification. Links are specified by the <linkHtml> construct, where the value for the href attribute of <linkHtml> (the target of the link) is the ID attribute value of a <id>, <paragraph>, <table>, <list>, <content>, <renderMultimedia>, etc., element. The stylesheet does not support the styleCode attribute of the <linkHtml> element; if a styleCode is needed for a link, this should be coded via the <content> element within the link as with other text.

6. Recent Major Changes in FPI Text

Information: A notation is provided for recent major changes in the FPI text.

Terminology: There is no controlled terminology for this information.

SPL location: The tag is located in the FPI text

XML details: The recent major text is tagged using the <content styleCode="xmChange">. For example:

<text>This is an example of text that is not changed.<content styleCode="xmChange">This is an example of text that is a recent major change</content>This is an example of changed text that is not considered a recent major change</text>

7. Highlights Text

Information: The actual Highlights of a rendered SPL is constructed from three sources: boilerplate text rendered directly from the stylesheet (e.g., "HIGHLIGHTS OF PRESCRIBING INFORMATION"), data elements inserted into the boilerplate text (e.g., Initial U.S. Approval <year>), and text blocks corresponding to each major highlights part (Highlights text). The Highlights text is captured for the following sections: Boxed Warning, Recent Major Changes, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations and Patient Counseling Information.

Terminology: There is no controlled terminology for this information.

SPL location: The text blocks for Highlights are coded with the <excerpt> <highlight> elements of the major section of labeling in which they are contained. For example, the Highlights for Indications and Usage are located with the Indications and Usage section of the labeling. The Highlights text is placed under the main section and not under subsections.

XML details: The text blocks of Highlight are coded with the <excerpt> <highlight> elements of the section in which they are contained. The following is sample coding:

```
<component>
   <section>
      <id root="xxxx"/>
      <code code="43685-7" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings and
      Precautions Section"/>
      <title>5 WARNINGS AND PRECAUTIONS </title>
         <excerpt>
            <highlight>
               <text>
                  <list listType="unordered">
                     <item>
```

```
                        Aplastic anemia has been observed in 8% of recipients and is irreversible in the
                        majority of patients who experience this. (<linkHtml
                        href="#Section_5.1">5.1</linkHtml>)
                    </item>
                    <item>
                        Monitor for hematological adverse reactions every 2 weeks through the second
                        month of treatment (<linkHtml href="#Section_5.2">5.2</linkHtml>)
                    </item>
                </list>
            </text>
        </highlight>
    </excerpt>
    <component>
        <section ID="Section_5.1">
            <id root="xxxx"/>
            <title>5.1 Aplastic anemia</title>
            <text>
                <paragraph>
                    Aplastic anemia has been observed in…..
                </paragraph>
            </text>
        </section>
    </component>
</section>
</component>
```

The following principles are illustrated by this example:

a. The <text> block for the Highlights is included as the <excerpt> <highlight> <text> children of the respective section. In the example above, the text block rendered in the highlights section is the child of the "Warnings and Precautions" section.
b. The coding of the highlights text block is not in a subsection.
c. The text block is rendered similar to any other text block, although in a location separate from its actual position in the rendered SPL document.
d. Links to the section or subsection where the primary content exists are explicitly entered in the Highlights text block.
e. Section numbering is included in the title of sections and subsections (e.g., '5' and '5.1', above).

Highlights boilerplate items include:

- Label title with information taken from the SPL header and drug listing data elements (e.g., product name, dosage form, route of administration).
- Highlights section titles taken from the FPI section LOINC codes.
- Adverse event reporting statement with information taken from the SPL header data elements
- Patient counseling statement with information taken from FPI section LOINC codes for patient information sections, specifically information for patient section (34076-0), SPL Medguide section (42231-1), SPL patient package insert section (42230-3) and SPL supplemental patient material (38056-8).

8. Highlights Data Elements

The Highlights Data Elements are described below.

8.1. Indications

Information: For each indication, the code for the intent of use, indication category and indication are provided.

Terminology: The HL7 terminology is used for Intent of Use. The LOINC code for Medical Problem is used for the indication category (note: the LOINC code for Medical Problem is also used for "Precondition Category"). Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are under the Indications and Usage section of labeling. If there is more than one indication, the data elements for each indication are under each respective subsection in the Indications and Usage section for the indication.

XML details: The indication is the <subject> of the <excerpt> <highlight> for the indication section or subsection. A <substanceAdminsitration> is the child of <subject>. Coding must contain the intent of use of treatment (<reason>) and the coding of the specific indication being treated (<indicationObservationCriterion>).

The <reason> for treatment is coded via the typeCode attribute of the reason element, e.g., <reason typeCode="TREAT">. The specific indication being treated is coded as the <code> and <value> of the <indicationObservationCriterion>. The following is sample coding for this section:

```
<section>
   <excerpt>
      <highlight>
         <subject>
            <substanceAdministration>
               <reason typeCode="xxxx">
                  <indicationObservationCriterion>
                     <code code="44100-6" codeSystem="2.16.840.1.113883.6.1" displayName="Medical
                     Problem"/>
                     <value xsi:type="CE" code="xxxx" codeSystem="xxxx" displayName="xxxx"/>
                  </indicationObservationCriterion>
               </reason>
            </substanceAdministration>
         </subject>
      </highlight>
   </excerpt>
</section>
```

Definitions of necessary elements:

1. <reason>: The <reason> element contains the typeCode attribute, which is the intent of use for the indication.

2. <indicationObservationCriterion>: The <indicationObservationCriterion> element contains the <code> and <value> children that specify that the indication is for a medical problem and the specific indication. The <code> element contains the code and codeSystem attributes; for the current implementation of SPL, the codeSystem is always coded as follows: <code code="44100-6" codeSystem="2.16.840.1.113883.6.1" displayName="Medical Problem"/>.

The <value> child of <indicationObservationCriterion> contains the code attribute for the actual indication and is coded as <value code="xxxx" codeSystem="xxx" displayName="xxxx"/>.

8.2. Maximum Dose

Information: The maximum dose is related to a specific amount of drug over a specific duration of time.

Terminology: UCUM is used for the units of both drug amount and duration of time.

SPL location: The maximum dose is coded under the sections or subsections where it is described. For example, if there is more than one indication, the maximum dose for each indication is under the subsection in the Indications and Usage section for the indication.

XML details: Maximum dose is specified as the <maxDoseQuantity> element, a child of <substanceAdministration>:

```
<highlight>
   <subject>
      <substanceAdministration>
      <maxDoseQuantity>
         <numerator value="xxx" unit="xxx"/>
         <denominator value="xxx" unit="xxx"/>
      </maxDoseQuantity>
      <reason…..>
      <precondition…>
      </substanceAdministration>
   </subject>
</highlight>
```

Definitions of necessary elements:

1. <maxDoseQuantity> may be coded as 'dose per unit time' of the <numerator> and <denominator> children. For example, "1000 mg per 24 hours" would be coded as:

```
<maxDoseQuantity>
   <numerator value="1000" unit="mg"/>
   <denominator value="24" unit="h"/>
</maxDoseQuantity>
```

8.3. Condition of Use

Information: There are three types of Condition of Use. One relates to a use of the drug in a selected subgroup of the larger population related to a characteristic of the patient such as the patient's age, race, sex or medical condition. The second relates to the use of the drug only in conjunction with another drug as an adjunct treatment. The third relates to the necessity of specific tests for the selection or monitoring of patients who need the drug.

Terminology: The Precondition Categories are LOINC codes. Sex and race codes are from the NCI Thesaurus. Age is represented by the low and high value. Age range has both a low and high value. The low value alone represents "Age greater than or equal to". The high value alone is used for "Age less than or equal to". Medical conditions are from the VA/KP Problem List subset. Treatments are from FDA SRS, FDA DRLS, and VA NDF-RT. Screening and monitoring tests are from LOINC.

SPL location: The Conditions of Use are coded under sections or subsections where they are described. For example, the data elements may be under the Indications and Usage section of labeling. If there is more than one indication, the data elements for each condition of use are under the subsection in the Indications and Usage section for that specific indication.

XML details: Conditions of Use are represented by the <precondition> and <protocol> children of <substanceAdministration>. The <precondition> and <protocol> are siblings of <reason>.

```
<subject>
    <substanceAdministration>
        <reason typeCode="xxxx">
            <indicationObservationCriterion>
            ….
            ….
            </indicationObservationCriterion>
        </reason>
        <precondition>
            …
        </precondition>
        <componentOf>
            <protocol>
                …..
            </protocol>
        </componentOf>
      </substanceAdministration>
</subject>
```

For the purpose of Highlights, children of <precondition> include: <observationCriterion>, and <substanceAdministrationCriterion>.

Definitions of necessary elements:

1. <observationCriterion>:

<observationCriterion> is used to code Conditions of Use based on a characteristic of the patient. For a patient characteristic, the <code> is the Precondition category and the <observationCriterion><value> is the specific characteristic of the patient. For example, an indication for a patient age 6 to 12 is coded as follows:

```
<precondition>
   <observationCriterion>
      <code code="30525-0" codeSystem="2.16.840.1.113883.6.1" displayName="AGE"/>
         <value xsi:type="IVL_PQ">
            <low value="6" unit="a"/>
            <high value="12" unit="a"/>
         </value>
   </observationCriterion>
</precondition>
```

2. <substanceAdministrationCriterion>

The <substanceAdministrationCriterion> is used for the co-administration of another agent as a precondition of use for a specified indication. This element identifies that the coded indication is for use of the product as an adjunct. An example of coding a <substanceAdministrationCriterion> is illustrated below:

```
<precondition>
   <substanceAdministrationCriterion>
      <consumable>
         <administrableMaterial>
            <playingMaterialKind>
               <code code="xxx" codeSystem="xxx" displayName="xxx"/>
            </playingMaterialKind>
         </administrableMaterial>
      </consumable>
   </substanceAdministrationCriterion>
</precondition>
```

The <code> child of <playingMaterialKind> i.e., <code code="xxx" codeSystem="xxx" displayName="xxx"/>, can be an ingredient using the FDA SRS code system, a drug product using the FDA DRLS code system, or a pharmacological class using the VA NDF-RT code system.

3. <monitoringObservation>

The <monitoringObservation> is used for specific tests for the selection or monitoring of patients who need the drug.

An example of coding a <monitoringObservation> is illustrated below:

```
<componentOf>
   <protocol>
      <component>
            <monitoringObservation>
               <code code="xxx-x" codeSystem="2.16.840.1.113883.6.1" displayName="xx"/>
            </monitoringObservation>
      </component>
   </protocol>
</componentOf>
```

8.4. Limitation of Use

Information: There are a number of reasons to limit the use of the drug such as contraindications. The Limitations of Use are based on characteristics of the patient such as the patient's age, race, sex or medical condition.

Terminology: The Limitation of Use/Issues categories are from the NCI Thesaurus. Precondition Categories are LOINC codes. Sex and race codes are from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset. Age is represented as a range with a low and high value. The low value alone represents "Age greater than or equal to". The high value alone is used for "Age less than or equal to".

SPL location: The Limitations of Use are coded under the sections or subsections where they are described. For example, the data elements may be under the Indications and Usage section of labeling if this is where the Limitation of Use is described.

XML details: Limitations of Use are coded as <issue> within the indication highlight excerpt. The following is an example of generic coding of an issue:

```
<section>
   <excerpt>
      <highlight>
         <subject>
            <substanceAdministration>
               <subjectOf>     <!-- Limitation of Use ->
                  <issue>
                     <code code="xxx" codeSystem="xxx" displayName="xxxx"/>
                     <subject>     <!—Example with an Observation Criterion ->
                        <observationCriterion>
                           <code code="xxx" codeSystem="xxx" displayName="xxxx"/>
                           <value xsi:type="CE"  code="xxxx" codeSystem="xxx" displayName="xxxx"/>
                        </observationCriterion>
                     </subject>
                  </issue>
               </subjectOf>
            </substanceAdministration>
         </subject>
      </highlight>
   </excerpt>
</section>
```

Each <issue> category is identified by the code attribute of the <code> child element of <issue> as in the following example:

```
<issue>
<code code="C50646" codeSystem="2.16.840.1.113883.3.26.1.1"
displayName="CONTRAINDICATION"/>
```

Each Limitation of Use is coded with a single <issue>. If two or more patient characteristics together represent a limitation of use, for example, the drug is contraindicated in a patient with both characteristic x AND characteristic y, the <subject> in the <issue> is repeated for each characteristic.

8.5. Drug Interaction

Information: Interactions have a contributing factor such as food or another drug and a consequence such as a medical condition.

Terminology: The Limitation of Use/Issue category code for interaction is used. Contributing factors are from FDA SRS (food or drug ingredients), FDA DRLS (specific drug products), VA NDF-RT (pharmacological class), and NCI Thesaurus (general substance such as "food"). Types of consequences are from the NCI Thesaurus. Pharmacokinetic effects are from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are coded under the section or subsection where the interaction is described. The same data elements may be represented in more than one place in the labeling.

XML details: Interactions include contributing factors and consequences.

8.5.1. Contributing factors

Interactions are coded as <issue>s. Each interaction is coded with a new <issue>. Similar to coding of <issue>s within indications, these are coded within the <excerpt> <highlight> of a section or subsection. For SPL, the subject of interactions is a <substanceAdministrationCriterion>.

```
<excerpt>
   <highlight>
      <subject>
         <substanceAdministration>
            <subjectOf>
               <issue>
                  <code code="xxx" codeSystem="xxx" displayName="xxx"/>
                     <subject>
                        <substanceAdministrationCriterion>
                           <consumable>
                              <administrableMaterial>
                                 <playingMaterialKind>
                                    <code code="xxx" codeSystem="xxx" displayName="xxx"/>
                                 </playingMaterialKind>
                              </administrableMaterial>
                           </consumable>
                        </substanceAdministrationCriterion>
                     </subject>
                     <risk>
                       ….. <!—described below →
                     </risk>
               </issue>
            </subjectOf>
```

```
            </substanceAdministration>
        </subject>
    </highlight>
</excerpt>
```

Definitions of necessary elements:

1. The <code> element child of issue contains the Limitation of Use/Issue category code for interaction.

2. The <code> element for <playingMaterialKind> reflects the 'contributing factor' for an interaction.

3. Each interaction is coded in a single <issue>. If two or more contributing factors together result a consequence, for example, Food x AND Food y taken with the Drug causes consequence z, the <subject> in the <issue> is repeated for each contributing factor. If two or more consequences occur together with an interaction, for example, Drug A taken with Drug B causes consequence x AND consequence y, the <risk> in the <issue> is repeated for each consequence. Multiple contributing factors and multiple consequences in a single interaction are handled the same way. On the other hand, if two or more contributing factors can independently result in the same consequence, for example Food x OR Food y taken with the Drug causes consequence z, there would be one <issue> for the Food x interaction and another <issue> for the Food y interaction.

8.5.2. Consequences

Consequences of an interaction are coded as <risk>, a sibling to the <subject> of an <issue>. This includes different types of consequences such as patient problems or pharmacokinetic effects. These are coded as <risk> <consequenceObservation>:

```
<issue>
    <subject>
    …..
    </subject>
    <risk>
        <consequenceObservation>
            <code code= "xxxx" codeSystem="xxxx" displayName="xxxx"/>
            <value xsi:type="CE"  code= "xxxx" codeSystem="xxx" displayName="xxxx"/>
        </consequenceObservation>
    </risk>
</issue>
```

Definitions of necessary elements:

1. <code> <value>. The <code> <value> pair identifies the actual outcome of the interaction where the <code> is the type of consequence and the <value> is the consequence.

2. Each interaction is coded in a single <issue>. If two or more contributing factors together result a consequence, for example, Food x AND Food y taken with the Drug causes consequence z, the <subject> in the <issue> is repeated for each contributing factor. Similarly, if two or more consequences occur together with an interaction, for example, Drug A taken with Drug B causes consequence x AND consequence y, the <risk> in the <issue> is repeated for each consequence. Multiple contributing factors and multiple consequences in a single interaction are handled the same way. On the other hand, if two or more contributing factors can independently result in the same consequence, for example Food x OR Food y taken with the Drug causes consequence z, there would be one <issue> for the Food x interaction and another <issue> for the Food y interaction..

8.6. Adverse Reaction

Information: Adverse Reactions have a medical condition consequence.

Terminology: The Limitation of Use/Issue category code for adverse reaction is used. The only type of consequence is a "Patient problem" from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are coded under the section or subsection where the adverse reaction is described. The same data elements may be represented in more than one place in the labeling.

XML details: Adverse reactions are coded as described for the consequence of an interaction. The <code> or type of consequence is a Patient Problem. The <value> is the consequence. Each Adverse Reaction is coded in a single <issue>.

8.7. Pharmacological Class

Information: Active ingredients and products may be described by pharmacological class.

Terminology: The VA NDF-RT is used for the pharmacological class.

SPL location: The pharmacological class for an ingredient is coded under the drug listing data element for the active ingredient. The pharmacological class for a product is coded under the Drug Listing data element for the manufactured medicine.

XML details: The pharmacological class of the ingredient is coded under <activeIngredient> and the pharmacological class of a product is coded under <manufacturedMedicine>.

8.7.1. Active ingredient

The pharmacological class of an active ingredient is the coded as <generalizedPharmaceuticalClass> a child of <activeIngredientSubstance><asSpecializedKind> as described below:

<manufacturedMedicine>

```
    <activeIngredient>
        <activeIngredientSubstance>
            <asSpecializedKind>
                <generalizedPharmaceuticalClass>
                    <code code="xxxx" codeSystem="xxx" displayName="xxx"/>
              </generalizedPharmaceuticalClass>
            </asSpecializedKind>
        </activeIngredientSubstance>
    </activeIngredient>
</manufacturedMedicine>
```

Definition of elements

1. An ingredient may have zero to many pharmacological classes. Each one is described with a new <asSpecializedKind> element.

8.7.2. Product

The pharmacological class of the overall <manufacturedMedicine> is coded as <generalizedPharmaceuticalClass> , a child of <specializedKind> as described below:

```
<manufacturedMedicine>
    <asSpecializedKind>
        <generalizedPharmaceuticalClass>
            <code code="xxxx" codeSystem="xxx" displayName="xxx"/>
         </generalizedPharmaceuticalClass>
    </asSpecializedKind>
</manufacturedMedicine>
```

Definition of elements

1. A product may have zero to many pharmacological classes. Each one is described with a new <asSpecializedKind> element.

9. Drug Listing Data Elements

Information: The data elements for drug listing that are found in the labeling are provided.

Terminology: FDA terminology is used for the proprietary, non proprietary and ingredient name. FDA Drug Registration and Listing System is used for the drug product and drug package code (National Drug Code), FDA Substance Registration System is used for the ingredient and active moiety code (Unique Ingredient Identifier). The NCI Thesaurus is used for dosage form and solid oral dosage form shape and color. NCI Thesaurus is also used for the DEA schedule, route of administration and unit of measure. Potency units are also from the Unified Codes for Units of Measure (UCUM).

SPL location: The drug listing data elements are in the first section of the SPL Body.

XML details: The drug listing data elements includes the drug product code, proprietary and nonproprietary name, dosage form, ingredient name, code and strength, active moiety name and code, package quantity, type and code, dosage form characteristics (appearance), DEA schedule, route of administration.

9.1. Product

The product consists of a product code, proprietary and nonproprietary name, and dosage form. These are children of <manufacturedMedicine>. The product code consists of the NDC labeler code and product code separated by a hyphen. The proprietary and nonproprietary names do not include any additional qualifiers such as trademarks or dosage forms.

```
<subject>
   <manufacturedProduct>
      <manufacturedMedicine>
        <code code="xxxx-xxxx" codeSystem="2.16.840.1.113883.6.69"/>
        <name>Proprietary name here</name>
        <formCode code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
        displayName="xxx"/>
        <asEntityWithGeneric>
           <genericMedicine>
              <name>non proprietary name here</name>
           </genericMedicine>
        </asEntityWithGeneric>
```

9.2. Active ingredient

The active ingredient includes the ingredient name and code, and strength, and the active moiety name and code. The element <activeIngredient> is a child of <manufacturedMedicine>. The strength is represented as a numerator and denominator and is described using UCUM and translated using FDA units of measure from the NCI Thesaurus. In the numerator and/or denominator, xsi:type=”URG_PQ” can be used to represent a range of strengths.

```
<activeIngredient>
        <quantity>
                <numerator value="xxx" unit="xxx">
                        <translation code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
                        displayName="xxx" value="xxx"/>
                </numerator>
                <denominator value="1" unit="1">
                        <translation code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
                        displayName="xxx" value="x"/>
                </denominator>
        </quantity>
        <activeIngredientSubstance>
                <code code="xxxxxxxxx" codeSystem="2.16.840.1.113883.4.9"/>
```

```
            <name>active ingredient name here</name>
            <activeMoiety>
                <activeMoiety>
                    <code code="xxxxxxxxxx" codeSystem="2.16.840.1.113883.4.9"/>
                    <name>active moiety name here</name>
                </activeMoiety>
            </activeMoiety>
        </activeIngredientSubstance>
</activeIngredient>
```

In most cases, the strength used is that for a single dose following the conventions in the table below. In the table, an example of "weight" is milligrams, an example of "volume" is milliliter, and an example of "each" is tablet)

Product	**Numerator unit**	**Denominator unit**
Oral solid	Weight	Each
Oral liquid	Weight	Volume
Oral powder for reconstitution with a known volume	Weight	Volume
Oral powder for reconstitution with a variable volume	Weight	Each
Suppository	Weight	Each
Injection liquid	Weight	Volume
Injection powder for reconstitution with a known volume	Weight	Volume
Injection powder for reconstitution with a variable volume	Weight	Volume
Inhaler powder	Weight	Each
Inhaler liquid	Volume	Each
Inhaler blister	Weight	Each
Topical cream or ointment	Weight	Weight
Topical gel or lotion	Weight	Volume
Transdermal patch	Weight	Each
Bulk liquid	Weight	Volume
Bulk solid	Weight	Weight

9.3. Inactive ingredient

The inactive ingredient includes the ingredient name and code, and strength. The element <inactiveIngredient> is a child of <manufacturedMedicine>. The strength, if needed, is represented as a numerator and denominator and is described using UCUM and translated using FDA units of measure from the NCI Thesaurus.

```
<inactiveIngredient>
        <quantity>
            <numerator value="xx" unit="xx">
                <translation code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
                displayName="xxx" value="xx" />
            </numerator>
            <denominator value="x" unit="xx">
```

```
                <translation code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
                displayName="xxx" value="x" />
            </denominator>
        </quantity>
        <inactiveIngredientSubstance>
            <code code="xxxxxxxxx" codeSystem="2.16.840.1.113883.4.9"/>
            <name>inactive ingredient name here</name>
        </inactiveIngredientSubstance>
</inactiveIngredient>
```

9.4. Packaging

The packaging includes the quantity of product in the package and the package type and code. The packaging is described using a combination of <quantity> and <containerPackagedMedicine> which are children of < manufacturedMedicine><asContent>. For example,

```
<asContent>
        <quantity>
            <numerator value="xxx" unit="x">
                <translation code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
                displayName="xxx" value="xxx"/>
            </numerator>
            <denominator value="x">
                <translation value="x"/>
            </denominator>
        </quantity>
        <containerPackagedMedicine>
            <code code="NDC here" codeSystem="2.16.840.1.113883.6.69"/>
            <formCode code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
            displayName="xxx"/>
        </containerPackagedMedicine>
</asContent>
```

The data element <asContent> can be nested to represent packages within other packages. If the packaging includes different drug products, use the <part> and <partMedicine> in addition to <quantity> and <containerPackagedMedicine>.

9.5. Route of Administration

A product may have one or more route of administration. The route of administration is described under <consumedIn> which is a child of <manufacturedMedicine> as illustrated in the following example of a drug that is given intravenously.

```
<consumedIn>
        <substanceAdministration>
```

```
        <routeCode code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1"
        displayName="xxx"/>
    </substanceAdministration>
</consumedIn>
```

9.6. DEA schedule

The DEA schedule, when applicable, is described under <policy> which is a child of <subjectOf> which is a child of <manufacturedMedicine> as illustrated in the following example of a drug that is schedule II.

```
<subjectOf>
    <policy classCode="DEADrugSchedule">
        <code code="xxx" codeSystem="2.16.840.1.112883.3.26.1.1" displayName="xx" />
    </policy>
</subjectOf>
```

9.7. Dosage Form Characteristics

The dosage form characteristics are used to describe the appearance of the solid oral dosage form and include the color, scoring, shape, size, coating, symbol and imprint code. These are all under <subjectOf> which is a child of <manufacturedMedicine>.

```
<subjectOf>
    <characteristic classCode="OBS">
        <code code="SPLCOLOR" codeSystem="2.16.840.1.113883.1.11.19255"/>
        <value code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="xxx"
        xsi:type="CE">
            <originalText>optional original color description text here</originalText>
        </value>
    </characteristic>
</subjectOf>

<subjectOf>
    <characteristic classCode="OBS">
        <code code="SPLSCORE" codeSystem="2.16.840.1.113883.1.11.19255"/>
        <value value="xx" xsi:type="INT"/>
    </characteristic>
</subjectOf>
<subjectOf>
    <characteristic classCode="OBS">
        <code code="SPLSHAPE" codeSystem="2.16.840.1.113883.1.11.19255"/>
        <value code="xxx" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="xxx"
        xsi:type="CE">
        <originalText>optional original shape description text here</originalText>
        </value>
```

```
        </characteristic>
</subjectOf>
<subjectOf>
        <characteristic classCode="OBS">
                <code code="SPLSIZE" codeSystem="2.16.840.1.113883.1.11.19255"/>
                <value unit="mm" value="xx" xsi:type="PQ"/>
        </characteristic>
</subjectOf>
<subjectOf>
        <characteristic classCode="OBS">
                <code code="SPLCOATING" codeSystem="2.16.840.1.113883.1.11.19255"/>
                <value value="xxx" xsi:type="BL"/>
        </characteristic>
</subjectOf>
<subjectOf>
        <characteristic classCode="OBS">
                <code code="SPLSYMBOL" codeSystem="2.16.840.1.113883.1.11.19255"/>
                <value value="xxx" xsi:type="BL"/>
        </characteristic>
</subjectOf>
<subjectOf>
        <characteristic classCode="OBS">
                <code code="SPLIMPRINT" codeSystem="2.16.840.1.113883.1.11.19255"/>
                <value xsi:type="ST">imprint separated by semicolon here</value>
        </characteristic>
</subjectOf>
```